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EXAMINER	
CORDERO GARCIA, MARCELA M	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/789,246	BETTENCOURT ET AL.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/28/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,10,11,17 and 25-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 10-11, 17, 25-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-5, 10-11, 17, 25-36 are pending in the application. Claims 1, 2, 17 have been amended. Claims 29-36 have been added.

This Office Action is in response to the reply received on April 28, 2008.

Any rejection from the previous office action, which is not restated here, is withdrawn.

Claims 1-5, 10-11, 17, 25-36 are presented for examination on the merits.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 10-11 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al. (Molecular Biotechnology, January 2002) in view of Sporeno et al. (Cytokine, 1994) and Gaberc-Porekar et al. (J Biochem Biophys Methods, 2001) and Pfeil et al. (Glycobiology, 2000).

Newton et al. teach a method for purifying a 6x histidine-tagged protein (e.g., page 65, section 3.1.d, and pages 67-69, sections 3.4 to 3.8) from a protein preparation (page 65, section 3.7), comprising:

(a) concentrating the tagged protein preparation with a negatively charged capture support, wherein the negatively charged capture support comprises heparin (page 68, section 3.8.1), comprising the steps of:

(i) contacting the protein preparation with the capture support (page 68, section 3.8.1);

(ii) washing the capture support with a capture support washing buffer of low ionic strength to remove interfering molecules but not the tagged protein from the capture support (page 68, section 3.8.2); and

(iii) eluting the tagged protein from the capture support with a capture support eluting buffer of high ionic strength; (page 68, section 3.8.3);

(b) purifying the tagged protein from the eluate of step (a) (iii) with a tag-specific affinity support, wherein the tag-specific affinity support comprises nickel nitrilotriacetic acid, comprising the steps of:

(i) contacting the eluate of step (a) (iii) with the tag-specific affinity support (page 68, section 3.8.1.2);

(ii) washing the affinity support with affinity support washing buffer of low ionic strength to remove some impurities but not the tagged protein from the affinity support (page 69, section 3.8.1.4); and

(iii) eluting the tagged protein from the affinity support with an affinity support eluting buffer (page 69, section 3.8.1.5).

The limitation of claim 2: --wherein the capture support washing buffer and the affinity support washing buffer comprise an ionic strength equivalent to about 50 mM to 150 mM salt equivalent reads upon Newton et al. page 74, Note 45, which teaches a low ionic strength 20mM Tris-HCl buffer, pH 7.5, containing 10% glycerol to wash the capture support (page 68, Section 3.8 and sub-section 2) [see 112 2nd rejection above]. The limitation of claim 3: --wherein the capture support eluting buffer comprises an ionic strength equivalent to at least about 500 mM—is taught, e.g., at page 68, Section 2.8, sub-section 3, which teaches 0-1.0 M NaCl gradient in the elution buffer. The limitation of claim 4: --wherein the capture support is applied to a column before or after contacting with the protein preparation—is taught, e.g., in page 68, Section 3.8, sub-section 1 and in page 73, Note 44, lines 1-6. The limitation of claim 5: --wherein the affinity support is applied to a column before or after contacting with the eluate of the capture support-- (e.g., page 68, Section 3.8.1, sub-sections 2-4). The limitation of claim 10: --wherein the affinity support eluting buffer comprises at least 50 mM imidazole-- is taught, e.g., in page 69, Section 3.8.1, sub-section 5). The limitations of claim 17: --

washing the capture support with a capture support washing buffer of an ionic strength equivalent to a concentration of about 50 mM to about 1 M to remove interfereing molecules but not the polyhistidine-tagged cytokine from the capture support—and – washing the affinity support with affinity support washing buffer of an ionic strength equivalent to a concentration of about 50 mM to about 1 M to remove some impurities but not the polyhistidine-tagged cytokine from the affinity support-- read upon Newton et al. which teach a low ionic strength 20mM Tris-HCl buffer, pH 7.5, containing 10% glycerol to wash the capture support (page 68, Section 3.8 and sub-section 2; page 74, Note 45) and Newton et al. page 69, 3.8.1 subsection 4, which teach 20mM Tris-HCL buffer pH 7.5 containing 10% glycerol and 0.8 mM imidazole to wash the affinity support, especially in the absence of a definition of "about". Additionally, Newton et al. teach that Ni^{2+}-NTA agarose affinity column should not be the first column used in the purification procedure because of the interference of contaminating proteins (e.g., Note 44 in page 73).

Newton et al. do not teach expressly purifying a 6x histidine tagged cytokine with a four-helix bundle.

Sporeno et al. teach a method of purifying a 6x histidine tagged cytokine (page 257, column 2, lines 17-22) with a four-helix bundle motif (e.g., page 255, column 2, lines with chelating Sepharose column charged with Ni^{2+} [i.e., a tag-specific affinity support column] from a protein preparation (e.g., abstract; page 261, column 1, lines 6-10).

Gaberc-Porekar teaches that efficient purification of recombinant proteins can be accomplished with engineered histidine affinity handles attached to the N- or C-terminus, especially in combination with the Ni^{2+}-NTA matrix, which selectively binds adjacent histidines. Since numerous neighboring histidine residues are uncommon among naturally occurring proteins, such oligo-histidine affinity handles form the basis for high selectivity and efficiency, often providing over 90% purity in one step (page 336, lines 16-22).

Neither reference expressly teaches a purifying a protein preparation derived from a mammalian cell culture, wherein the polyhistidine tagged cytokine is present in the protein preparation at a concentration of no more than 2 mg/L.

Pfeil et al. teach chromatography on heparin-agarose (e.g., page 803, column 2, 4th paragraph) of a protein preparation derived from a mammalian cell culture supernatant (as in instant claims 29-30, 33-34, e.g., page 803, column 2, 3rd paragraph) and subsequent affinity chromatography (e.g., page 804, column 1, 2nd and 3rd paragraph).

Neither reference teaches: applying to a transiently expressed polyhistidine tagged cytokine, near 100% capture with greater than 99% purity as in claims 31-32 and 35-36.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Newton by applying expressly to the 6x histidine tagged cytokine with a four-helix bundle motif of Sporeno et al. by adding a heparin column step previous the tag-specific affinity support column step because, as

taught by Newton et al. in Note 44, page 73, Ni^{2+}-NTA agarose affinity column should not be the first column used in the purification procedure because of the interference of contaminating proteins.

The skilled artisan would have been motivated to do so because Newton et al. teach that a 2-step process using a heparin column before the metal chelating column eliminates the majority of contaminating proteins during purification of polyhistidine proteins (see Newton et al., e.g., abstract and page 73, section 44) and because Newton et al. teach Ni^{2+}-NTA agarose should not be the first column used in the purification procedure because of the interference of contaminating proteins (e.g., page 73, Note 44, last 5 lines). Obtaining a product with lesser contaminants is a clear motivation in the art. Even though Sporeno does not expressly indicate the desirability of further purification, Gaberc-Porekar et al. teach the use of oligo-histidine affinity handles in recombinant proteins form the basis for high selectivity and efficiency during separations with Ni^{2-}-NTA affinity columns, often providing over 90% purity in one step (page 336, lines 16-22). Please note that about 90% purity would still allow for further purification. There would have been reasonable expectation of success, given that both proteins were obtained from bacterial cells, were tagged with histidine, and could be purified via metal chelating columns (i.e., tag-specific affinity support columns). The adjustment of particular conventional working conditions (e.g., adding an extra separation processes, optimizing the ionic strength of buffers, measuring transiently expressed proteins within such purification method) is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled

artisan. As such, it would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g., selection of column separation steps, optimization of buffer ionic strength for washing/elution, applying to mammalian cell expressed proteins, including transiently expressed proteins, measuring capture and purity %), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.". In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2145.05). One would have been motivated to determine all optimum and operable conditions in order to achieve the highest yield of the highest purity product in the most efficient manner. One would have had a reasonable expectation for success because such modifications are routinely determined and optimized in the art through routine experimentation.

From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 1, 17 and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al. (Molecular Biotechnology, January 2002) in view of Sporeno et al. (Cytokine, 1994), Gaberc-Porekar et (J Biochem Biophys Methods,

2001), Lovenberg et al. (US 6,239,268), Soussi-Gounni et al. (Molecular mechanisms in allergy and clinical immunology, 2001) and Pfeil et al. (Glycobiology, 2000).

Newton et al., Sporeno et al., Gaberc-Porekar et al. Pfeil et al. are relied upon as above.

Lovenberg et al. teach human (column 2, lines 8-9) cytokine receptors (e.g., column 1, lines 18-20) which are polyhistidine tagged and are purified on a NTA nickel chelating column (e.g., column 5, lines 27-49).

Soussi-Gounni et al. teach that IL-9 may play a prominent role in asthma pathology (e.g., abstract). IL-9 is a member of the 4-helix bundle cytokine family (page 575, line 12), human cytokine IL9RA gene and human IL-9R gene product is a protein composed of 522 amino acids (e.g., page 576, column 1, lines 9-24). Soussi et al. also teach that IL9RA may be involved in down-regulating IL-9R function. (page 576, column 1, lines 30-34).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to separate recombinant human cytokines such as those of Soussi et al. by tagging with polyhistidine as taught by Lovenberg et al., Newton et al. and Sporeno et al. The skilled artisan would have been motivated to do so to obtain a purified product, e.g., to study the role of IL9RA in asthma. Obtaining a product with lesser contaminants is a clear motivation in the art. Even though Sporeno et al. and Lovenberg et al. do not expressly indicate the desirability of further purification, Gaberc-Porekar et al. teach the use of oligo-histidine affinity handles in recombinant proteins form the basis for high selectivity and efficiency during separations with Ni^{2-}-NTA affinity

columns, often providing over 90% purity in one step (page 336, lines 16-22). Please note that about 90% purity would still allow for further purification. There would have been reasonable expectation of success, given that the various type proteins of Sporeno et al. Lovenberg et al., Newton et al. and Gaberc-Porekar were recombinantly-produced, tagged with histidine, and could be purified via metal chelating columns (i.e., tag-specific affinity support columns), including those with 4-helix bundles. The adjustment of particular conventional working conditions (e.g., electing human cytokine IL9RA within such separation method) is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan. As such, it would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g., protein to be purified), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.". In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2145.05). One would have been motivated to determine all optimum and operable conditions in order to achieve the highest yield of the highest purity product in the most efficient manner in order to, e.g., study the role of IL9RA in allergic asthma. One would have had a reasonable expectation for success because such modifications are routinely determined and optimized in the art through routine experimentation.

From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary s-kill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicants' arguments

As indicated in the Example 1, the claimed method is surprisingly useful for the purification of minute quantities of human cytokines, providing near 100% capture for the polyhistidine-tagged cytokine and greater than 99% final purity as judged by silver stain SDS gels. Neither Sporeno et al. nor Newton et al. teach or suggest such levels of yield and purity or that such levels can be achieved by the presently claimed method.

Applicants respectfully traverse the rejection but have nevertheless amended the claim to a protein preparation that is derived from a mammalian cell culture, wherein the polyhistidine-taged cytokine is present in the protein preparation at a concentration of no more than 2 mg/L, said method comprising, inter alia: (a) concentrating the polyhistidine-tagged cytokine from the eluate of step (a)(iii) with a tag specific affinity support. Dependent claims further defined the invention by reciting: wherein the polyhisdistidine-tagged cytokine is poly-histidine-tagged human IL9ra (claims 26 and 28); wherein the protein preparation is derived from a mammalian cell culture supernatant (claims 30 and 34), and is nearly 100% captured form the protein preparation with greater than 99% purity (claims 32 and 36); or wherein the

polyhistidine-tagged cytokine is transiently expressed in the mammalian cell culture (claims 31 and 35).

Despite the reported success in using the Ni2+ matrix to purify polyhistidine-tagged proteins that were abundantly expressed in bacteria, the same success has not been easily attainable in purifying proteins expressed in low quantities, a problem often seen in mammalian cell expression systems. Applicants described in the specification that at low concentrations, the binding of a polyhistidine-tagged protein to the Ni2=+ matrix is often thermodynamically unfavorable. See, page 1, last paragraph of the specification. As a result, less than 25% of the target protein may be bound out of culture supernatant to the affinity matrix. Id. Applicants discovered that implementing a chromatography-based concentration step before the affinity purification step utilizing a heparin capture support greatly improves the binding themodynamics of the target protein to the Ni2+ affinity matrix. See page 2, last paragraph.

In contrast, the nature of the problem to be solved by Newton is completely different. Newton merely relates to a method of purifying polyhistidine-tagged RNase single-chain antibody fusion protein, which is expressed in large quantities in bacteria cells and accumulated in bacterial inclusion bodies. Thus, Newton at best teaches a method for purifying an abundantly expressed recombinant protein from the inclusion bodies in a bacterial expression system. It is in this context that Newton advidsed against direct application of a protein preparation to the Ni2+ column. See page 73, note 44 of Newton. Newton, however, does not provide any guidance as to how to purify a recombinant protein expressed in low quantities in a mammalian expression system.

Newton does not teach or suggest that the method disclosed has general applicability to all target proteins, much less to a recombinant protein expressed in minute quantities in a mammalian expression system. In fact, Newton states that the best method for purification needs to be determined for each specific target protein. See page 68, point No. 5, under section 3.8 of Newton.

It would not have been obvious to one skilled artisan to apply the 2-step purification scheme of Newton to arrive at the claimed invention because Newton does not recognize nor appreciate the unique problems in purifying recombinant proteins expressed in low quantities in mammalian cells. Newton merely relates to purification of abundantly expressed proteins in bacterial inclusion bodies. Newton does not concer purification of a polyhistidine-tagged cytokine from a mammalian cell culture lysate or supernatant, much less improving the binding thermodynamics of the recombinant protein to the Ni$+ matrix. Newton certainly does not teach or suggest a method for purifying a polyhistidine-tagged cytokine expressed in low quantities in mammalian cells, wherein the polyhistidine tagged cytokine is nearly 100% capture from the protein preparation with greater than 99% purity.

Sporeno does not cure the defect. Sporeno merely relates to a single column affinity purification scheme for purifying a polyhistidine-tagged OncM protein in a bacterial expression system. Sporeno teaches over-expressing the target protein in bacterial cells, isolating inclusion bodies, refolding the protein and applying the protein preparation directly onto a Ni2+ column. Similar to Newton, Sporeno does not recognize the unique problems faced in purifying polyhistidine-tagged proteins expressed in low

quantities in mammalian cells. Sporeno does not provide any guidance regarding how to purify a polyhistidine-tagged cytokine expressed in low quantities in mammalian cells, let alone a purification that allows nearly quantitative recovery with greater than 99% purity.

Equally unhelpful is Gaberc-Porekar, which constitutes a general review of immobilized-metal affinity chromatography. Similar to Newton and Sporeno, Gaberc-Porekar does not recognize or appreciate the unique problems in purifying polyhistidine-tagged proteins expressed in mammalian cell culture in low quantities nor provide any guidance in solving the unique challenges face by the instant application.

In addition, Applicants unexpectedly discovered that the claimed method surprisingly overcame the difficulties in purifying low quantities of human cytokines and provided nearly 100% capture of the polyhistidine-tagged cytokines with greater than 99% final purity as judged by silver stain SDS gels. See, for example, page 14 and 15 of the specification. Such unexpected results are not taught or suggested in any one of the cited art, alone or in combination.

With respect to the second rejection, contrary to Examiners' assertion, Lovenberg merely mentions in passing the purification of a cytokine receptor, not a cytokine. Col. 5, lines 27-49. Soussi-Gounni merely studies the activity of IL9 and does not teach or suggest purification thereof. In view of the unique difficulties in purifying polyhistidien-tagged protein expressed in mammalian cells in low quantitiets, one of skill in the art would not have used the 2-column purification scheme similar to that of

Newton's to purify IL9ra expressed in mammalian cells in low quantities with a reasonable expectation of success.

Response to arguments

Applicant's arguments have been fully considered but they are not persuasive for the reasons set forth above and because Applicant fails to substantiate the unexpected results arguments with any evidence. Further application fails to provide any substantive reason that there would no expectation of success for the purification of polyhistidine-tagged cytokines specifically in mammalian cell cultures using the 2-step chromatography taught by the cited references [e.g., Newton], and specifically in mammalian cell cultures (see above). Further, it is also noted that the references cited do not teach away from using lower concentrations and/or other cell cultures. Therefore, the invention is prima facie obvious over the references.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCELA M. CORDERO GARCIA whose telephone number is (571)272-2939. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654

/Marcela M Cordero Garcia/
Examiner, Art Unit 1654

MMCG 07/08